Journal of Surgical Oncology 61:262–266 (1996)

Clinical Manifestations in Patients With Hereditary Nonpolyposis Colorectal Cancer

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The clinical manifestations of 1,042 Japanese patients with nonpolyposis colorectal cancer who underwent a resection between 1972 and 1992 at the National Kyushu Cancer Center were examined. Hereditary nonpolyposis colorectal cancer (HNPCC) was found in 39 (3.7%) patients. Some characteristic findings in HNPCC cases included early age of onset, a preponderance of right colon cancers, an increased frequency of colorectal cancers, and a favorable survival. Metachronous (postoperative) colorectal cancers developed significantly more often in cases with HNPCC than in those without (12.8% vs. 1.8%, $P = 0.0001$). Metachronous (postoperative) extracolonic cancers tended to develop more often in cases with HNPCC than in those without (10.2% vs. 3.5%, $P = 0.053$). In cases with HNPCC, the mean interval between the initial surgery and the diagnosis of the second cancer was 61 months (range; 12–153 months). These findings thus indicate the importance of routine and long-term follow-up to identify any second lesions, especially in patients with HNPCC.

KEY WORDS: second primary cancer, HNPCC, colorectal cancer

INTRODUCTION

According to reports, families with a high incidence of colorectal cancer are found in the absence of familial adenomatosis coli [1–9]. A study of such families can thus provide valuable information about environmental or genetic risk factors of colorectal cancer. Hereditary nonpolyposis colorectal cancer (HNPCC) is one of the diseases found in such families. HNPCC has no reliable clinical marker, but advances in molecular biology have led to the discovery of the replication error phenomena occurring in 80% of HNPCC tumors and the mismatch repair genes that are responsible for HNPCC. In some families, molecular diagnosis may be possible. The diagnosis is generally highly dependent upon family history. An investigation of the clinical manifestations in HNPCC is thus important to identify such cases. Regarding the biological behavior of HNPCC, a predominance of diploid tumors has been reported [10,11]. However, this point remains controversial.

In this study, we compare the clinicopathologic characteristics, DNA content, and occurrence of the second primary cancers between the cases with and without HNPCC, and discuss the importance of the identification and surveillance of cases with HNPCC.

MATERIALS AND METHODS

The family histories of 1,042 Japanese patients with nonpolyposis colorectal cancer who underwent a resection at the National Kyushu Cancer Center between 1972 and 1992 were examined. All cases were studied according to the "General rules for clinical and pathological studies on cancer of colon, rectum and anus" [12]. The clinicopathologic characteristics and incidence of the occurrence of the second primary cancers were compared between the groups with and without HNPCC.

A patient demonstrating the following criteria for diagnosis, proposed at the 34th meeting of the Japanese Soci-

Accepted for publication November 27, 1995.
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ety of Cancer of the Colon and Rectum (Tokushima, Japan, February 1991), was regarded as having HNPCC: (1) three or more colorectal cancer cases (including the proband) among first-degree relatives (parents, siblings, and children), (2) two or more colorectal cancer cases (including the proband) among first-degree relatives and one or more of the following features—age <50 years; right colon cancer proximal to the splenic flexure; synchronous or metachronous colorectal cancers; synchronous or metachronous extracolonic cancers.

In addition, the DNA content in 248 of the 1,042 cases with colorectal cancer was analyzed and compared between the groups with and without HNPCC. The DNA content of fresh frozen materials that had been surgically resected was measured as described previously [13]. Briefly, single cell suspensions were prepared by the method of Sasaki et al. [14]. After staining by propidium iodide, a total of 10,000 nuclei were counted by a FACScan flow cytometer (Beckton Dickinson, San Jose, CA). The DNA index (DI) was calculated at the ratio of the fluorescent intensity (DNA content) of the G1/0 peak of the tumor cells and then was compared with that for the G1/0 peak of the diploid tumors (normal cells) [15]. Tumors with a DI of 1.0–1.1 were designated as diploid, whereas tumors with a DI > 1.1 were designated as aneuploid. Tumors with diploid and aneuploid subpopulations were designated as aneuploid. Eight samples with a coefficient of variations >8% were excluded from this study.

Statistical Analysis

The data were analyzed statistically using either the Chi-square or Students' *t*-test. The survival rates were calculated by the Kaplan-Meier method. Differences in survival rates were evaluated using the generalized Wilcoxon test. Significant differences were regarded as present at $P < 0.05$.

RESULTS

Cases with HNPCC were found in 39 (3.7%) of the 1,042 patients with nonpolyposis colorectal cancer. Families with two affected relatives were the most common (32/39, 82.1%), followed by families with three affected relatives (6/39, 15.4%) and a family with four affected relatives (1/39, 2.5%).

Table I shows the clinicopathologic characteristics between the groups with and without HNPCC. The mean age was significantly younger in cases with HNPCC than in those without (55.9 years old vs. 61.1 years old, $P = 0.0122$). Right colon cancers were found significantly more often in cases with HNPCC than in those without (59.0% vs. 16.8%, $P = 0.0001$). However, there were no differences with regard to sex, histology, cancer stage, or curability between the two groups.

Regarding the DNA content, diploidy was found in 4 (40%) of 10 cases with HNPCC and in 67 (28%) of 238 cases without. A DI (mean ± SD) was 1.43 ± 0.50 in cases with HNPCC and 1.45 ± 0.37 in those without. However, none of these differences were significant.

Table II shows the incidence of cases with synchronous or metachronous colorectal cancers and extracolonic cancers in the cases with colorectal cancer. Synchronous colorectal cancers were found more often in cases with HNPCC than in those without (20.5% vs. 5.8%, $P =$

TABLE I. Clinicopathologic Characteristics Between Cases With and Without HNPCC

Clinicopathologic characteristics[a]		Cases without HNPCC[b] (n = 10)	Cases with HNPCC[b] (n = 39)	*P*-value
Sex	Male	440 (43.9)	17 (43.6)	NS
	Female	563 (56.1)	22 (52.4)	
Age (yr)	Mean	61.1 ± 12.0	55.9 ± 17.0	0.0122
	Range	19–92	15–84	
Sites	C,A,T	169 (16.8)	23 (59.0)	0.0001
	D,S,R	834 (83.2)	16 (41.0)	
Histology	Well	731 (72.9)	30 (76.9)	NS
	Mod	196 (19.5)	7 (17.9)	
	Por,Muc	50 (5.0)	2 (5.2)	
	Others	26 (2.6)	0 (0.0)	
Stage	0	57 (5.7)	2 (5.1)	NS
	I	150 (15.0)	4 (10.3)	
	II	307 (30.6)	16 (41.0)	
	III	308 (30.7)	13 (33.3)	
	IV	181 (18.0)	4 (10.3)	
Curability	A	781 (77.9)	35 (89.7)	NS
	B	78 (7.8)	1 (2.6)	
	C	144 (14.3)	3 (7.7)	

[a]C = cecum; A = ascending colon; T = transverse colon; D = descending colon; S = sigmoid colon; R = rectum; Well = well-differentiated adenocarcinoma; Mod = moderately differentiated adenocarcinoma; Por = poorly differentiated adenocarcinoma; Muc = mucinous carcinoma; Curability A = no residual tumors with a high possibility of cure; Curability B = no residual tumors but not evaluable as "Curability A or C"; Curability C = definite residual tumors.
[b]Numbers in parentheses are percentages.
NS = no significant difference.

TABLE II. Synchronous or Metachronous Colorectal Cancers and Extracolonic Cancers in Cases With Colorectal Cancer

Colorectal cancers and extracolonic cancers	Cases without HNPCC[a] (n = 1,003)	Cases with HNPCC[a] (n = 39)	*P*-value
Synchronous			
Colorectal cancers	58 (5.8)	8 (20.5)	0.0002
Extracolonic cancers	43 (4.3)	2 (5.1)	NS
Metachronous (preoperative)			
Colorectal cancers	7 (0.7)	2 (5.1)	0.0416
Extracolonic cancers	64 (6.4)	2 (5.1)	NS
Metachronous (postoperative)			
Colorectal cancers	18 (1.8)	5 (12.8)	0.0001
Extracolonic cancers	35 (3.5)	4 (10.2)	0.053

[a]Numbers in parentheses are percentages.
NS = no significant difference.

TABLE III. Metachronous (Postoperative) Colorectal Cancers and/or Extracolonic Cancers in 8 Cases With Hereditary Nonpolyposis Colorectal Cancer

Cases	Sex	Age	Site of cancer		Interval
			First cancer	Second cancer	
1	F	39	Rectum	Ascending colon	77 mo
2	F	79	Transverse colon	Ascending colon	60 mo
3	F	83	Cecum	Sigmoid colon	59 mo
4	M	65	Transverse colon	Rectum[a]	12 mo
5	M	67	Sigmoid colon Stomach	Transverse colon Ureter	39 mo
6	M	47	Rectum	Stomach	74 mo
7	F	33	Ascending colon	Uterus	153 mo
8	M	37	Cecum Descending colon	Stomach[a]	17 mo

[a]Mucosal cancer.

0.0002). There was no significant difference in the incidence of synchronous extracolonic cancers between the two groups (5.1% vs. 4.3%). Metachronous (preoperative) colorectal cancers were found significantly more often in cases with HNPCC than in those without (5.1% vs. 0.7%, $P = 0.0416$). However, no significant differences were observed in the incidence of metachronous (preoperative) extracolonic cancers between the two groups (5.1% vs. 6.4%). Metachronous (postoperative) colorectal cancers developed in 5 (12.8%) of the 39 cases with HNPCC, whereas they developed in 18 (1.8%) of the 1,003 cases without HNPCC, and the rate of the former was significantly higher than the latter ($P = 0.0001$). Metachronous (postoperative) extracolonic cancers developed in 4 (10.2%) of the 39 cases with HNPCC, and in 35 (3.5%) of the 1,003 cases without HNPCC. The rate of the former also tended to be higher than the latter ($P = 0.053$). One HNPCC patient demonstrated both a metachronous colon cancer and extracolonic cancer, whereas one of the cases without HNPCC had both a metachronous colon cancer and extracolonic cancer. The incidence of the cases with metachronous (postoperative) colorectal cancers and/or extracolonic cancers was 20.5% (8/39) in the cases with HNPCC and 5.2% (52/1003) in the cases without HNPCC, and the rate of the former was significantly higher than the latter ($P = 0.0002$).

Table III shows the eight HNPCC cases with metachronous (postoperative) colorectal cancers and/or extracolonic cancers. Colorectal cancers occurred between 12 months and 77 months (mean: 49 months). Extracolonic cancers occurred between 18 months and 153 months (mean: 70 months). Among the eight cases, early cancers were found in two, whereas advanced cancers were found in six. An early cancer was defined when cancer was limited to the mucosa or submucosa. A mucosal rectal cancer and mucosal gastric cancer were diagnosed 12 months and 17 months later based on postoperative routine barium enema and gastrography, respectively. For the other six cases, postoperative routine examinations

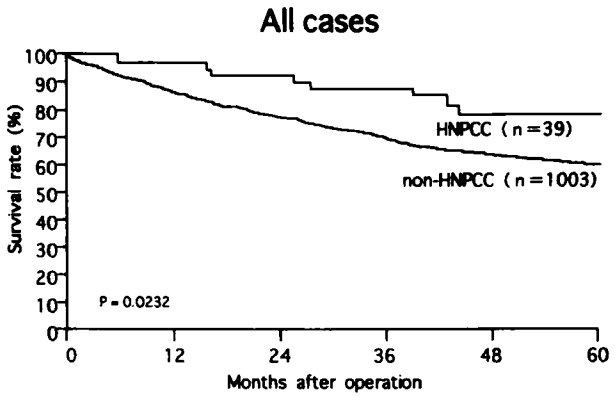

Fig. 1. Survival time in all cases was significantly longer in the cases with hereditary nonpolyposis colorectal cancer (HNPCC) than in those with non-HNPCC.

(once a year), such as barium enema or gastrography, were not performed for various reasons.

The survival time in all cases was significantly longer in the cases with HNPCC than in those without ($P = 0.0236$) (Fig. 1). When they were divided by curability, survival time in the curative cases tended to be longer in the former cases than in the latter ($P = 0.085$). When they were divided by stage, survival time in the cases with stage III cancers tended to be longer in the former cases than in the latter ($P = 0.0617$).

DISCUSSION

HNPCC has been variously defined. According to Lynch et al. [5], HNPCC is comprised of the following: (1) cancer family syndrome (CFS) or Lynch syndrome II, which shows an early-onset proximal colonic cancer preponderance and other associated extracolonic adenocarcinomas, particularly endometrial carcinoma, and (2) hereditary site-specific colon cancer (HSSCC) or Lynch syndrome I, which shows all of the same characteristics, except for extracolonic cancer. HNPCC also has been

defined by the criteria proposed by the International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer (ICG-HNPCC) [16,17]. These are known as the "Amsterdam criteria" and are as follows: (1) three or more relatives with histologically verified colorectal carcinoma, one of whom is a first-degree relative of the other two, (2) colorectal carcinoma involving at least two generations, and (3) one or more colorectal carcinoma cases diagnosed at an age younger than 50 years.

We performed this study according to the criteria proposed at the 34th meeting of the Japanese Society of Cancer of the Colon and Rectum. In our survey, an early age of onset, a preponderance of right colon cancers, an increased frequency of colorectal cancers, an increased frequency of second cancers, and a longer survival were characteristic in cases with HNPCC.

With regard to histology, Lynch et al. [18] investigated 110 colorectal carcinomas in 95 HNPCC patients. The colorectal carcinomas in HNPCC contained a large number of poorly differentiated adenocarcinomas. In addition, Mecklin et al. [19] found that the cancers in HNPCC cases appeared to have a mucinous component when compared to controls. In the present study, we found no significant difference in the histology between the groups with and without HNPCC.

DNA flow cytometry of nuclei obtained from colorectal carcinomas revealed a predominance of diploid tumors in HNPCC [10,11]. Frei [11] reported that the prolonged survival after discovery of malignancy in such families may be explained in part by a predominance of diploid tumors. In the present study, we found no significant difference in the DNA content between the groups with and without HNPCC. However, the number of the samples investigated was small. A further study is thus needed to obtain a final conclusion.

Cases with HNPCC have been reported to have a relatively indolent course with a prolonged survival in comparison to other colorectal cancers [20]. In the present study, we also found that survival was longer in cases with HNPCC than in those without. When the patients were divided by stage, survival tended to be longer in the cases with stage III cancers. When the patients were divided by curability, survival tended to be longer in the curative cases. However, there was a significant difference regarding the patient age and tumor site between the two groups. This discrepancy of survival may thus be due to a difference in the distribution of both patient age and tumor site. A further study is thus needed based on the patients with the same age and same tumor site.

With regard to the second cancers after surgery in the cases with HNPCC, Lynch et al. [21], in a 3-year follow-up of 34 patients with HNPCC whose initial colon carcinoma was treated with a segmental resection or hemicolectomy, found nine carcinomas and nine adenomas (2 with severe dysplasia). At 10 years, the chance of developing a second colon cancer was 50%, whereas the chance of a third was 20%.

In the present study, second primary cancers developing after surgery occurred significantly more often in cases with HNPCC than in those without (20.5% vs. 5.1%). The mean interval between the first surgery and the diagnosis of the second primary cancers was 61 months. In addition, early rectal cancer and early gastric cancer were found 12 months and 17 months later based on routine postoperative barium enema and gastrography, respectively.

These findings therefore suggest the importance of a routine and long-term follow-up for the occurrence of any second cancers, especially in patients with HNPCC.

ACKNOWLEDGMENTS

We thank Brian T. Quinn for his critical comments.

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